EXHIBIT 2

Effects of 1,3-Dimethylamylamine and Caffeine Alone or in Combination on Heart Rate and Blood Pressure in Healthy Men and Women

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Abstract

Background: The use of 1,3-dimethylamylamine (geranamine), alone and in combination with caffeine, is becoming widespread within the dietary supplement industry. To our knowledge, no data are available concerning the effects of oral geranamine intake on heart rate (HR) and blood pressure in individuals. **Methods:** Ten young healthy men and women ingested 1 of 5 conditions on different days using a double-blind, randomized, crossover design. The following were ingested after a 10-hour overnight fast: 250 mg caffeine (C), 50 mg geranamine (G 50 mg), 75 mg geranamine (G 75 mg), 250 mg caffeine + 50 mg geranamine (C + G 50 mg), and 250 mg caffeine + 75 mg geranamine (C + G 75 mg). Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate pressure product (RPP) were measured pre-ingestion and at 30, 60, 90, and 120 minutes post-ingestion. Plasma norepinephrine (NE) and epinephrine (EPI) were measured pre-ingestion and at 60 and 120 minutes post-ingestion. **Results:** Heart rate was unaffected by treatment, but blood pressure and RPP were higher with geranamine, generally in a dose-dependent manner. The peak percent change from pre-ingestion in SBP (~20%), DBP (~17%), and RPP (~9%) was noted with C + G 75 mg at 60 minutes post-ingestion. Plasma NE and EPI were relatively unaffected by treatment. **Conclusion:** We report for the first time that acute ingestion of 1,3-dimethylamylamine alone and in combination with caffeine results in an increase in SBP, DBP, and RPP without an increase in HR. The largest increase is observed at 60 minutes post-ingestion of C + G 75 mg. These changes cannot be explained by circulating NE and EPI.

Keywords: caffeine; geranamine; blood pressure; heart rate; catecholamines

Introduction

Regardless of economic conditions, dietary supplements are a multimillion-dollar-per year industry, according to the *Nutrition Business Journal*.[1] Many products contain natural (ie, herbal) and synthetic stimulants, such as guarana, ma huang, Kola nut, phenylethylamine, and caffeine. One recent addition to the stimulant category is geranium extract, which has been noted to be present in small amounts in geranium oil.[2] This ingredient has received a great deal of attention in recent years and is included in multiple dietary supplements targeting weight/fat loss, as well as enhanced physical performance. Although anecdotal reports of improved focus and mood, enhanced exercise performance, and decreased appetite are common, to our knowledge, no studies have attempted to verify these claims using controlled laboratory procedures. Moreover, while only scant data are available pertaining to the hemodynamic effects of intravenous and nasal inhalation delivery of this ingredient in animals[3,4] and humans (as noted in documentation from Eli Lilly & Co. regarding methylhexamine [Forthane™]),

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respectively, no studies to our knowledge have determined the effect of acute oral intake of geranium extract on heart rate (HR) and blood pressure in human subjects. This is important information to obtain considering the widespread use of this ingredient in many dietary supplements that are currently sold on the worldwide market.

A review of information obtained from various online sources, including 1 scientific article,[2] indicates that geranium extract may be a component of the *Pelargonium graveolens* plant, with anecdotal health benefits noted on various Web sites, as well as antioxidant[5] and other potential health benefits noted in the scientific literature.[6] In much the same way as caffeine is associated with both positive[7–10] and potentially negative[11–15] effects on human health and function, the same may be true for geranium extract.

The action of geranium extract appears as a simple aliphatic amine functioning as a norepinephrine (NE) reuptake inhibitor and/or NE-releasing agent. According to patent data available via the US Patent and Trademark Office (document 2,350,318) entitled "Aminoalkanes" (dated April 9, 1942), geranium extract (noted as 2-amino-4-methylhexane) stimulates smooth muscle and may act as a vasoconstrictor. In addition to 2-amino-4-methylhexane, other common chemical names of this agent include 1,3-dimethylamylamine, 1,3-dimethylpentylamine, methylhexaneamine, 4-methyl-2-hexylamine, and geranamine (Proviant Technologies, Inc., Champaign, IL), which was trademarked in 2005 (US trademark number: 78542697).

Aside from the above information and the anecdotal reports from individuals using geranamine, very little is known about this ingredient, despite its widespread availability and use. Therefore, the purpose of this investigation was to determine the effect of geranamine intake at 2 different dosages of practical relevance, with and without the addition of caffeine (as caffeine is commonly combined with geranamine in many dietary supplements), on HR and blood pressure. We included a caffeine-only condition for comparison purposes, as the effects of caffeine on HR and blood pressure are well described.[16] Based on the potential vasoconstrictor properties of geranamine, we also measured plasma NE and epinephrine (EPI) in response to treatment. The study involved a single oral serving of each condition by healthy men and women, with observation for a 2-hour post-ingestion period.

Materials and Methods

Subjects

Young, healthy, exercise-trained men (n = 5) and women (n = 5) participated in this investigation. All subjects completed a medical history and physical activity questionnaire in order to determine eligibility. No subject was a smoker, used smokeless tobacco products, or had diagnosed cardiovascular (eg, hypertension) or metabolic disease. Six subjects reported using caffeine daily through consumption of coffee (n = 5) or soda (n = 1). The mean intake for these 6 subjects was estimated at 220 mg per day. Three other subjects reported occasional use of caffeine through consumption of coffee or soda (eg, once per week). One subject reported never using caffeine. Men and women were considered exercise trained, as they performed combined aerobic and anaerobic exercise for 6 ± 3 and 7 ± 3 hours per week, respectively, for the past several years. Subject descriptive characteristics are presented in Table 1. All experimental procedures were performed in accordance with the Declaration of Helsinki. The University of Memphis Human Subjects Committee approved all experimental procedures (H10–45), and subjects provided verbal and written consent prior to participating in this study.

Testing and Conditions

All testing procedures described below were identical for all 5 test days. Subjects reported to the laboratory in a 10-hour fasted state, and all testing was completed in the morning hours. The time of testing was matched for subjects for all conditions. Subjects were instructed to not exercise for the 24 hours prior to each test day. On arrival to the laboratory, subjects were asked to void and then rest quietly for 10 minutes in a seated position. Following this quiet rest period, HR (via radial artery palpation for 60 seconds by 2 trained technicians) and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured via auscultation using a dual earpiece stethoscope, and a blood

Table 1. Demographics of Study Participants

Variable	Men	Women
Age, y	26 ± 5	23 ± 3
Height, cm	174 ± 4	167 ± 7
Weight, kg	88 ± 11	73 ± 17
BMI, kg/m^2	29 ± 3	26 ± 6
Body fat, %	16 ± 6	24 ± 8
Waist, cm	90 ± 9	76 ± 12
Hip, cm	106 ± 6	102 ± 10
Resistance exercise training, y	8 ± 7	4 ± 3
Resistance exercise, h/wk	5 ± 3	2 ± 1
Aerobic exercise training, y	3 ± 4	3 ± 3
Aerobic exercise,[a] h/wk	1 ± 1	5 ± 4

Data are mean ± standard deviation.
[a]No statistically significant differences noted in any variable ($P > 0.05$) except for hours per week aerobic exercise ($P = 0.05$).

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sample was obtained pre-ingestion. Subjects were then provided their assigned condition and ingested it in the presence of an investigator. Heart rate, SBP, and DBP were recorded again at 30, 60, 90, and 120 minutes post-ingestion. Rate pressure product (RPP) was calculated as an indication of myocardial work, using the equation: HR × SBP. Blood was again obtained at 60 and 120 minutes post-ingestion. During and following each condition, subjects were asked to report any effects that were felt. Subjects rested quietly during the entire 2-hour period of data collection and consumed no food. However, water was allowed *ad libitum* and matched for subjects on the days of testing (mean intake, 517 mL).

The 5 conditions were provided in random order, using a double-blind, crossover design. The conditions were encapsulated, taken with water, and consisted of: 250 mg caffeine (C), 50 mg geranamine (G 50 mg), 75 mg geranamine (G 75 mg), 250 mg caffeine + 50 mg geranamine (C + G 50 mg), and 250 mg caffeine + 75 mg geranamine (C + G 75 mg). The dosages used in the present design are common for both caffeine and geranamine, as determined via current dietary supplement product labels and human subject reports assessed via various internet sites. The geranamine (1,3-dimethylamylamine HCL) was purchased from Waseta International Trading Co., Ltd. (Shanghai, China), and the caffeine (caffeine anhydrous) was purchased from Hi-Tech Pharmaceuticals, Inc. (Norcross, GA). Certificates of analysis for each ingredient indicated purity.

It should be noted that no placebo condition was included in the present design, which may be considered to be a limitation. However, we justify our omission of a placebo condition in the following manner. First, we know from our prior work and from the work of others that our measured variables are very stable in men and women when they are not receiving an active condition.[17–19] That is, little to no change in HR or blood pressure is noted when men and women simply rest quietly in a controlled environment. Second, our main objective in the present design was to determine the acute effect of geranamine alone and when combined with caffeine on HR and blood pressure, and to compute the percent change from pre-ingestion in these variables. We believe that the present design adequately provides these data. It should also be noted that the present design only attempted to investigate the acute (2-hour) effects of caffeine and geranamine alone or in combination, and at the dosages provided. Therefore, data from the present investigation do not provide information related to the effects of these conditions at times distant to 2 hours post-ingestion, or in regards to dosages less than or greater than what was provided here. Moreover, our data relate only to a single ingestion and do not provide clinical information related to long-term use of either ingredient alone or in combination—in particular in regards to the development of hypertension over time. It is possible that attenuation in response might be observed following long-term use, as a "tolerance" to regular treatment may be observed. This is known to occur in some but not all individuals who regularly consume caffeine—in terms of selective outcome measures.[20] Likewise, a tachyphylaxis has been demonstrated for geranamine.[3]

Blood Collection and Biochemistry

A total of 3 venous blood samples (7 mL per draw) were taken from subjects' forearm via needle and Vacutainer® (BD Diagnostics, Franklin Lakes, NJ). Blood was immediately processed in a refrigerated centrifuge to obtain plasma (4°C for 15 minutes at 2000 × g). Plasma samples were then stored at –70°C. Norepinephrine and EPI were determined using an enzyme-linked immunosorbent assay (2-CAT ELISA, BA 10–1500; Rocky Mountain Diagnostics, Colorado Springs, CO) following the instructions of the manufacturer (Labor Diagnostika Nord GmbH & Co., Nordhorn, Germany). In this competitive ELISA, NE and EPI were extracted by using a cis-diol–specific affinity gel, acylated, and then derivatized enzymatically. Standards were used to calculate unknown values of NE and EPI within each plasma sample, and controls were used to verify assay precision.

Statistical Analysis

Heart rate and blood pressure data were analyzed using a 5 (condition) × 5 (time) analysis of variance (ANOVA). Analysis of variance was also performed for change from baseline (pre-ingestion) for HR and blood pressure, and data are presented in figure format to provide a visual representation of the overall response for each variable measured. Epinephrine and NE data were analyzed using a 5 (condition) × 3 (time) ANOVA. Tukey's post-hoc tests were performed when necessary. Due to our small sample size and the novelty of this initial work focused on geranamine, no major attempt was made to determine sex-specific differences in the response to treatment. However, we did perform a correlation analysis (for each condition independently) on sex, body weight, and the percent change in SBP and DBP at 60 minutes post-ingestion (the time of peak response for most conditions). Statistical significance was set at $P \leq 0.05$. The analyses were done using JMP statistical software version 4.0.3 (SAS Institute, Cary, NC). Data are presented

at mean ± standard error of mean (SEM), except for subject characteristics, which are presented as mean ± standard deviation (SD).

Results

Subject Comments

All 10 subjects successfully completed all test days. The conditions were generally well tolerated; however, the following comments were provided by subjects: For C, 1 of 10 subjects reported feeling fatigued. For G 50 mg, 1 of 10 subjects reported feeling cold; 1 of 10 subjects reported feeling fatigued; and 2 of 10 subjects reported feeling lightheaded. For G 75 mg, 1 of 10 subjects reported that his/her nose and face felt "tingly." For C + G 50 mg, 1 of 10 subjects reported a lack of appetite and feeling very "awake." For C + G 75 mg, 1 of 10 subjects reported feeling lightheaded with somewhat labored breathing; 1 of 10 subjects reported that his/her ears felt "stopped up"; 1 of 10 subjects reported feeling "buzzed" with some chest tightness; 1 of 10 subjects reported that his/her nose had "cleared up" following ingestion.

Heart Rate and Blood Pressure Data (Absolute and Percent Change)

With regards to absolute data for HR, no interaction ($P = 1.00$), condition ($P = 0.95$), or time effect ($P = 0.11$) was noted, with values decreasing slightly following ingestion of the conditions. Absolute data are presented in Table 2. Regarding the percent change data for HR (Figure 1), no interaction effect ($P = 0.99$) was noted. However, a condition effect ($P = 0.02$) was noted, with C + G 50 mg higher than C and C + G 75 mg ($P < 0.05$). A time effect ($P = 0.0004$) was also noted, with 30, 60, 90, and 120 minutes lower than pre-ingestion ($P < 0.05$).

With regards to absolute data for SBP, no interaction effect ($P = 0.75$) was noted. However, a condition effect ($P = 0.0001$) was noted, with G 75 mg and C + G 75 mg greater than C, and C + G 75 mg greater than G 50 mg ($P < 0.05$). A time effect ($P < 0.0001$) was also noted, with 60, 90, and 120 minutes > 30 minutes and pre-ingestion ($P < 0.05$). Absolute data are presented in Table 3. Regarding the percent change data for SBP (Figure 2), no interaction effect ($P = 0.21$) was noted. However, a condition effect ($P < 0.0001$) was noted, with G 75 mg and C + G 75 mg greater than C; C + G 75 mg greater than G 50 mg and C + G 50 mg; and G 75 mg greater than G 50 mg ($P < 0.05$). A time effect ($P < 0.0001$) was also noted, with 60, 90, and 120 minutes greater than 30 minutes and pre-ingestion ($P < 0.05$).

With regards to absolute data for DBP, no interaction effect ($P = 1.00$) or condition effect ($P = 0.19$) was noted. However, a time effect ($P = 0.0004$) was noted, with 60, 90, and 120 minutes greater than pre-ingestion ($P < 0.05$). Absolute data are presented in Table 4. Regarding the percent change data for DBP (Figure 3), no interaction effect ($P = 1.00$) or condition effect ($P = 0.38$) was noted. However, a time effect ($P < 0.0001$) was noted, with 60, 90, and 120 minutes greater than pre-ingestion ($P < 0.05$).

With regards to absolute data for RPP, no interaction ($P = 1.00$) or time effect ($P = 0.26$) was noted. However, a condition effect ($P = 0.04$) was noted, with C + G 75 mg greater than C ($P < 0.05$). Absolute data are presented in Table 5. Regarding the percent change data for RPP (Figure 4), no interaction effect ($P = 0.65$) was noted. However, a condition effect ($P < 0.0001$) was noted, with G 75 mg, C + G 50 mg, and C + G 75 mg greater than C; C + G 50 mg greater than G 50 mg ($P < 0.05$). A time effect ($P = 0.006$) was also noted, with 120 minutes greater than 30 minutes and pre-ingestion; 60 minutes was greater than 30 minutes ($P < 0.05$).

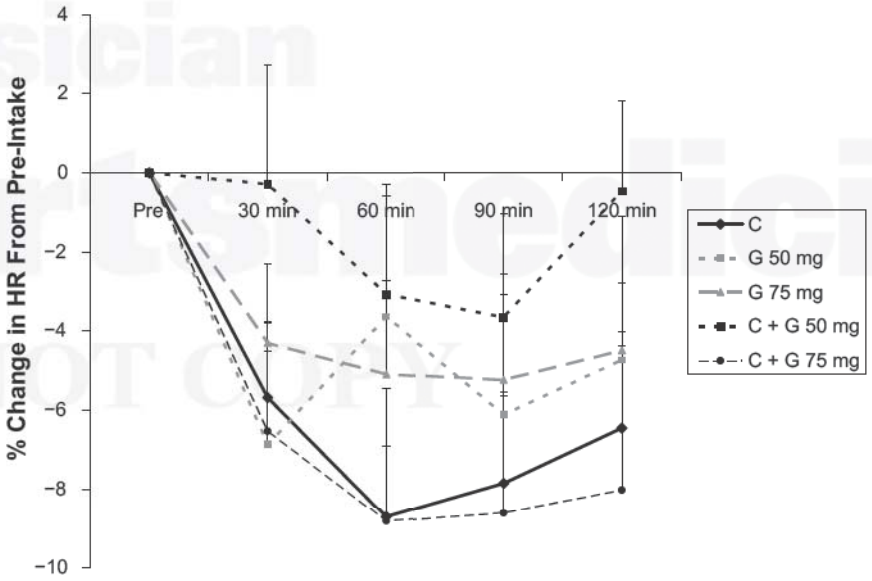
The correlation analysis indicated a significant negative correlation between body weight and percentage change in SBP for G 50 mg ($r = -0.85$; $P = 0.002$). No other significant correlations were noted for any other condition with regards

Table 2. Heart Rate (bpm) Pre- and Post-Ingestion of Caffeine and Geranamine Alone or in Combination

Time	Caffeine 250 mg	Geranamine 50 mg	Geranamine 75 mg	Caffeine 250 mg + Geranamine 50 mg	Caffeine 250 mg + Geranamine 75 mg
Pre-ingestion	60 ± 3	60 ± 2	59 ± 3	59 ± 3	62 ± 2
30 min	56 ± 3	56 ± 2	56 ± 2	58 ± 2	58 ± 2
60 min	55 ± 3	57 ± 2	56 ± 3	57 ± 2	56 ± 3
90 min	55 ± 3	56 ± 3	56 ± 3	56 ± 2	56 ± 3
120 min	56 ± 3	57 ± 3	57 ± 2	58 ± 2	57 ± 3

Data are mean ± standard error of mean.
No condition × time interaction effect ($P = 1.00$).
No condition effect ($P = 0.95$).
No time effect ($P = 0.11$).

Figure 1. Percent change in heart rate from pre-intake of caffeine and geranamine alone or in combination.



Data are mean ± standard error of mean.
No condition × time interaction effect ($P = 0.99$).
Condition effect ($P = 0.02$); caffeine 250 mg + geranamine 50 mg different than caffeine 250 mg and caffeine 250 mg + geranamine 75 mg ($P = 0.05$).
Time effect ($P = 0.0004$); 30 min, 60 min, 90 min, 120 min different than pre-ingestion ($P < 0.05$).
Abbreviations: C, caffeine 250 mg; G 50 mg, geranamine 50 mg; G 75 mg, geranamine 75 mg; C + G 50 mg, caffeine 250 mg + geranamine 50 mg; C + G 75 mg, caffeine 250 mg + geranamine 75 mg.

to body weight or sex ($P > 0.05$). No significant correlations were noted for body weight or sex, for any condition, in relation to percentage change in DBP ($P > 0.05$).

Catecholamine Data

With regards to NE, no interaction ($P = 0.99$) or condition effect ($P = 0.99$) was noted. However, a time effect ($P = 0.01$) was noted, with 60 minutes lower than pre-ingestion and 120 minutes ($P < 0.05$). For EPI, no interaction ($P = 0.59$), condition ($P = 0.20$), or time effect ($P = 0.06$) was noted, but values generally increased at 60 minutes (6%) and 120 minutes (23%) compared with pre-ingestion. Data are presented in Table 6.

Discussion

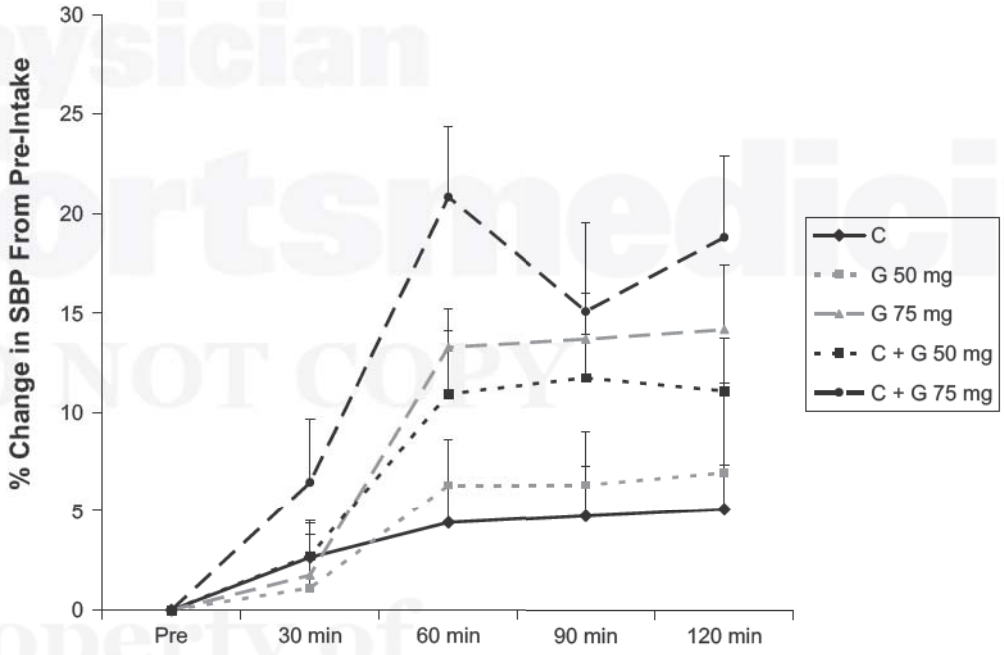
Data from the present study indicate that oral geranamine intake by healthy men and women results in an increase in SBP, DBP, and RPP without impacting HR. This is supported by observed changes in both absolute (SBP, DBP) and percent change values (SBP, DBP, RPP). The addition of caffeine to geranamine (at a dosage of 50 mg) results in an additive effect on the percent increase in RPP (Figure 4), but does not increase the response for any other variable, assuming the same dosage, in a statistically significant manner. The greatest increase in SBP and DBP is observed between 60 minutes and 90 minutes post-ingestion, in particular with the C + G 75 mg condition. These changes cannot be

Table 3. Systolic Blood Pressure (mm Hg) Pre- and Post-Ingestion of Caffeine and Geranamine Alone or in Combination

Time[b]	Caffeine 250 mg	Geranamine 50 mg	Geranamine 75 mg[a]	Caffeine 250 mg + Geranamine 50 mg	Caffeine 250 mg + Geranamine 75 mg[a]
Pre-ingestion	117 ± 3	121 ± 4	118 ± 4	119 ± 4	119 ± 3
30 min	120 ± 4	122 ± 4	120 ± 3	122 ± 4	126 ± 4
60 min	122 ± 4	128 ± 4	133 ± 5	131 ± 4	143 ± 5
90 min	122 ± 3	128 ± 4	134 ± 4	133 ± 4	136 ± 4
120 min	123 ± 5	128 ± 4	132 ± 4	132 ± 4	141 ± 5

Data are mean ± standard error of mean.
No condition × time interaction effect ($P = 0.75$).
[a]Condition effect ($P = 0.0001$); geranamine 75 mg and caffeine 250 mg + geranamine 75 mg different than caffeine 250 mg; caffeine 250 mg + geranamine 75 mg different geranamine 50 mg ($P < 0.05$).
[b]Time effect ($P < 0.0001$); 60, 90, and 120 minutes different than 30 minutes and pre-ingestion ($P < 0.05$).

Figure 2. Percent change in systolic blood pressure from pre-intake of caffeine and geranamine alone or in combination.



Data are mean ± standard error of mean.
No condition × time interaction effect ($P = 0.21$).
Condition effect ($P < 0.0001$); geranamine 75 mg and caffeine 250 mg + geranamine 75 mg different than caffeine 250 mg; caffeine 250 mg + geranamine 75 mg different than geranamine 50 mg and caffeine 250 mg + geranamine 50 mg; geranamine 75 mg different than geranamine 50 mg ($P < 0.05$).
Time effect ($P < 0.0001$); 60, 90, 120 minutes different than 30 minutes and pre-ingestion ($P < 0.05$).
Abbreviations: C, caffeine 250 mg; G 50 mg, geranamine 50 mg; G 75 mg, geranamine 75 mg; C + G 50 mg, caffeine 250 mg + geranamine 50 mg; C + G 75 mg, caffeine 250 mg + geranamine 75 mg; SBP, systolic blood pressure.

explained by the increase in NE and EPI, as the caffeine and geranamine appear to drive this response directly, as opposed to indirectly by increasing NE and EPI. Finally, there does not appear to be any significant influence of sex or body weight on these changes, with a possible exception of body weight being negatively correlated to the change in SBP following ingestion of G 50 mg. To our knowledge, these are the first data in human subjects to describe the effects of oral geranamine intake on HR and blood pressure.

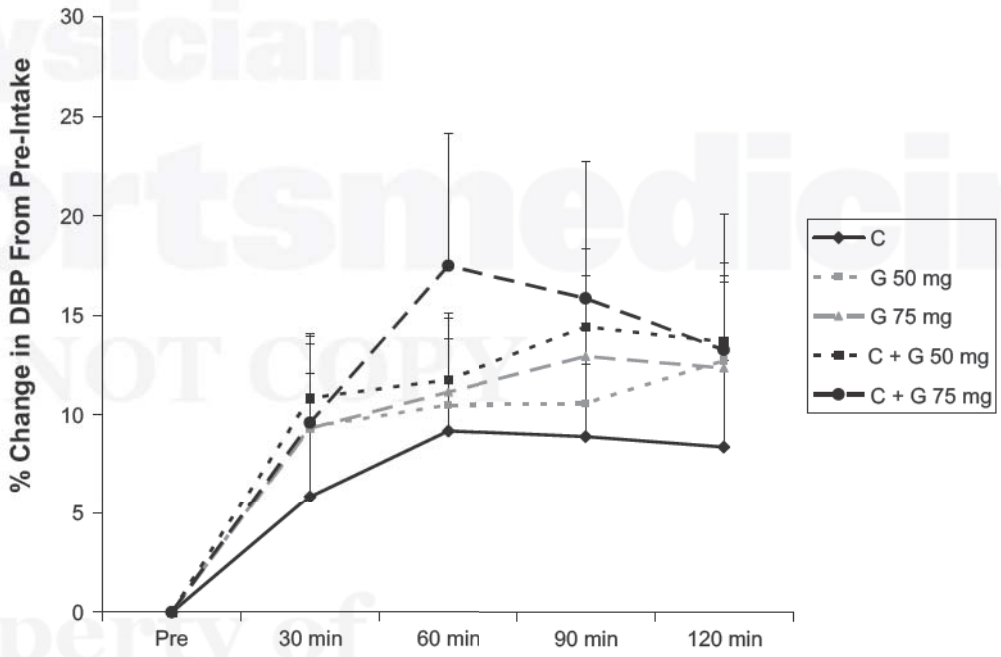
Other studies involving caffeine alone,[16,21,22] as well as caffeine combined with agents such as yohimbine and PEA[17] have noted similar findings for HR, SBP, and DBP as in the present study. Although we were somewhat surprised by a decrease in HR with all treatments (when expressed as a percent change from pre-ingestion), some prior studies involving caffeine have noted similar findings.[23,24] Based on the lack of an observed increase in HR, it is likely that the explanation for the increase in blood pressure involves an increase in total peripheral resistance and/or an increase in stroke volume. Indeed, the vasoconstriction effect of geranamine is supported by Eli Lilly's trademark application for Forthane™, which states "vasoconstrictor preparation."

Table 4. Diastolic Blood Pressure (mm Hg) Pre- and Post-Ingestion of Caffeine and Geranamine Alone or in Combination

Time[a]	Caffeine 250 mg	Geranamine 50 mg	Geranamine 75 mg	Caffeine 250 mg + Geranamine 50 mg	Caffeine 250 mg + Geranamine 75 mg
Pre-ingestion	70 ± 3	69 ± 4	70 ± 4	68 ± 3	71 ± 3
30 min	74 ± 4	75 ± 4	76 ± 2	75 ± 3	77 ± 3
60 min	76 ± 3	76 ± 4	77 ± 3	76 ± 3	83 ± 3
90 min	76 ± 3	76 ± 4	79 ± 3	78 ± 3	71 ± 3
120 min	75 ± 3	77 ± 4	78 ± 3	77 ± 3	80 ± 4

Data are mean ± standard error of mean.
No condition × time interaction effect ($P = 1.00$).
No condition effect ($P = 0.19$).
[a]Time effect ($P = 0.0004$); 60, 90, and 120 minutes different than pre-ingestion ($P < 0.05$).

Figure 3. Percent change in diastolic blood pressure from pre-intake of caffeine and geranamine alone or in combination.



Data are mean ± standard error of mean.
No condition × time interaction effect ($P = 1.00$).
No condition effect ($P = 0.38$).
Time effect ($P < 0.0001$); 30, 60, 90, and 120 min different than Pre ($P < 0.05$).
Abbreviations: C, caffeine 250 mg; G 50 mg, geranamine 50 mg; G 75 mg, geranamine 75 mg; C + G 50 mg, caffeine 250 mg + geranamine 50 mg; C + G 75 mg, caffeine 250 mg + geranamine 75 mg; DBP, diastolic blood pressure.

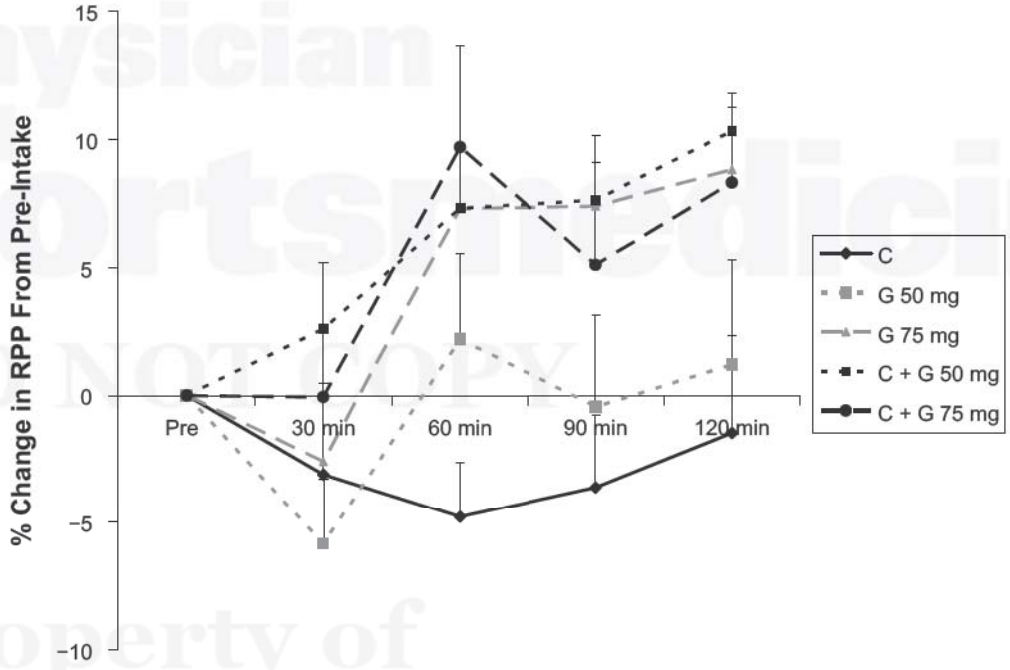
It is well accepted that an increase in catecholamine hormones may promote an increase in both vasoconstriction and cardiac contractility (promoting the above-mentioned effects). However, the greatest increase in NE and EPI was noted with caffeine intake alone, which was also associated with the smallest increase in blood pressure. Therefore, other mechanisms aside from circulating catecholamines must be responsible for our findings. This is likely mediated by a direct effect of geranamine on SBP as opposed to an indirect effect mediated by increasing NE and EPI. Although it has been reported that geranamine is less active than EPI in elevating blood pressure in animals,[3] the comparative effects in human subjects is unknown. Aside from a direct effect of geranamine, it is possible that an increase in sympathetic nervous system activity could be observed, irrespective of circulating catecholamines. Finally, it is also possible that catecholamine secretion at times other than 60 and 120 minutes post-ingestion could have influenced our findings. For example, we noted the peak increase in both SBP and DBP between 60 and 90 minutes post-ingestion, but we also measured blood NE and EPI at 60 minutes post-ingestion. Perhaps NE and EPI were peaking at times prior to the 60-minute post-ingestion measure, and hence mediating the increase in SBP and DBP observed at the 60-minute post-ingestion time. Considering our limited blood sampling, this possibility cannot be ruled out. Future studies attempt-

Table 5. Rate Pressure Product Pre- and Post-Ingestion of Caffeine and Geranamine Alone or in Combination

Time	Caffeine 250 mg	Geranamine 50 mg	Geranamine 75 mg	Caffeine 250 mg + Geranamine 50 mg	Caffeine 250 mg + Geranamine 75 mg[a]
Pre-ingestion	7015 ± 376	7294 ± 459	6996 ± 376	6993 ± 443	7356 ± 380
30 min	6817 ± 472	6824 ± 406	6776 ± 338	7122 ± 433	7271 ± 375
60 min	6669 ± 381	7348 ± 349	7539 ± 489	7427 ± 401	7995 ± 338
90 min	6770 ± 426	7157 ± 355	7492 ± 385	7420 ± 355	7595 ± 254
120 min	6897 ± 443	7247 ± 331	7567 ± 366	7688 ± 496	7929 ± 387

Data are mean ± standard error of mean.
No condition × time interaction effect ($P = 1.00$).
[a]Condition effect ($P = 0.04$); caffeine 250 mg + geranamine 75 mg different than caffeine 250 mg ($P < 0.05$).
No time effect ($P = 0.26$).

Figure 4. Percent change in rate pressure product from pre-intake of caffeine and geranamine alone or in combination.



Data are mean ± standard error of mean.
No condition × time interaction effect ($P = 0.65$).
Condition effect ($P < 0.0001$); geranamine 75 mg, caffeine 250 mg + geranamine 50 mg, and caffeine 250 mg + geranamine 75 mg is different than caffeine 250 mg; caffeine 250 mg + geranamine 50 mg different than geranamine 50 mg ($P < 0.05$).
Time effect ($P = 0.006$); 120 min different than 30 min and Pre; 60 min different than 30 min ($P < 0.05$).
Abbreviations: C, caffeine 250 mg; G 50 mg, geranamine 50 mg; G 75 mg, geranamine 75 mg; C + G 50 mg, caffeine 250 mg + geranamine 50 mg; C + G 75 mg, caffeine 250 mg + geranamine 75 mg; RPP, rate pressure product.

ing to describe the mechanistic effects of geranamine in relation to blood pressure may consider multiple and frequent sampling times for a more complete analysis of circulating catecholamines.

In the lay press, it has been suggested that geranamine may have similar functional properties as ephedrine. Ephedrine has been studied previously and noted to exhibit mixed results in terms of HR and blood pressure, with most work indicating a moderate increase in these variables.[25–28] For example, a study by Haller et al[27] noted an increase in SBP of 14 mm Hg at 90 minutes post-ingestion with a combination of caffeine (200 mg) and ephedrine alkoloids (20 mg).[27] Interestingly, the HR peaked by 15 beats per minute above baseline at 6 hours post-ingestion. This is an important consideration in relation to the present data, as we ceased measurement at 2 hours post-ingestion. Although it is possible that HR,

Table 6. Plasma NE and EPI Pre- and Post-Ingestion of Caffeine and Geranamine Alone or in Combination

Time	Caffeine 250 mg	Geranamine 50 mg	Geranamine 75 mg	Caffeine 250 mg + Geranamine 50 mg	Caffeine 250 mg + Geranamine 75 mg
NE ($pg \cdot mL^{-1}$)					
Pre	306 ± 34	339 ± 47	328 ± 46	327 ± 46	321 ± 41
60 min[a]	254 ± 32	267 ± 32	275 ± 49	272 ± 37	293 ± 41
120 min	383 ± 44	335 ± 40	340 ± 49	338 ± 38	340 ± 27
EPI ($pg \cdot mL^{-1}$)					
Pre	51 ± 8	72 ± 10	70 ± 8	47 ± 9	71 ± 8
60 min	56 ± 8	63 ± 12	73 ± 9	69 ± 10	71 ± 9
120 min	84 ± 7	80 ± 12	83 ± 11	60 ± 10	77 ± 10

Data are mean ± standard error of mean.
No condition × time interaction effect for NE ($P = 0.99$) or EPI ($P = 0.59$).
No condition effect for NE ($P = 0.99$) or EPI ($P = 0.20$).
[a]Time effect for NE ($P = 0.01$); 60 min lower than pre-ingestion and 120 min ($P < 0.05$).
No time effect for EPI ($P = 0.06$).
Abbreviations: EPI, epinephrine; NE, norepinephrine.

SBP, or DBP could have been increased at times beyond our 2-hour post-ingestion period, percent change data presented in Figures 1 to 3 indicate that values (for the most part) were stable or returned toward baseline by 120 minutes. Indeed, future work is needed to determine the longer-term effects of geranamine alone and in combination with caffeine on HR and blood pressure. Investigators interested in this area of research are encouraged to pursue additional studies, as very few data are currently available pertaining to this ingredient, despite its widespread use.

Of potential concern in relation to our findings for geranamine is the increase in blood pressure in response to treatment, in particular at a dosage of 75 mg. Even when combined with 250 mg of caffeine, a dosage of 50 mg of geranamine did not result in as significant an increase in SBP, and a similar increase in DBP, as compared with 75 mg of geranamine alone (when presented as percent change from pre-ingestion; Figures 2, 3). This finding for geranamine was rather uniform, although the magnitude of effect varied across subjects, which is typical for many nutrients and drugs. Although acute ingestion of geranamine does appear to increase blood pressure, it should be made clear that data from this study do not provide us with the needed evidence to comment on the effect of chronic geranamine ingestion with regards to blood pressure elevation. That is, at present there is no evidence to indicate that routine use of this agent results in hypertension. This is underscored by the reported tachyphylaxis for this agent.[3] Despite this, based on the acute elevation in blood pressure observed following intake of geranamine by healthy men and women, it would likely be prudent for individuals with known hypertension to avoid use of this agent. Additional work is needed to determine the potential impact of regular geranamine ingestion on HR and blood pressure over time, in addition to the clinical relevance that any noted changes in these variables might have.

Conclusion

We report for the first time that acute oral geranamine intake by healthy men and women results in a significant increase in blood pressure, without impacting HR. The effect appears dose dependent, in particular for SBP, with a greater increase at 75 mg compared with 50 mg. The addition of caffeine to geranamine (at a dosage of 50 mg) increases the percent change from pre-ingestion in RPP, but does not influence other variables in a statistically significant manner. The changes in HR and blood pressure cannot be explained by circulating NE and EPI. Future studies are needed to determine what, if any, change in resting HR and blood pressure may be noted with chronic ingestion of geranamine.

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Conflict of Interest Statement

Richard J. Bloomer, PhD discloses conflicts of interest with Advanced Oral Technologies, Kaneka Nutrients, Formulife, and USPLabs. Innocence C. Harvey, BS, Tyler M. Farney, MS, Zach W. Bell, BS, and Robert E. Canale, MS disclose no conflicts of interest.

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